UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,922	04/05/2001	David E. Comings	1954-332	3812

6449 7590 08/23/2004

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,922	COMINGS, DAVID E.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68,70,71,74 and 75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68, 70-71, 74-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers June 23, 2004. Currently, claims 68, 70, 71, 74-75 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the cancellation of several claims and amendments to the claims to require particular mutations.

4. This action is FINAL.

Priority

5. This application claims priority to provisional application 60/195,312, filed April 10, 2000.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 68, 70, 71, 74-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method of determining a risk of an individual for attention deficit hyperactivity disorder (ADHD) by determining whether a subject has at least 2 or 3 or 4 non-wild-type alleles from at least one gene selected from TPH, PNMT, ADOA2A, NOS3 and NAT1 and to methods of determining for each of the genes a wild-type or non-wild type allele.

The specification teaches analyzing numerous genes for their association with ADHD. Figure 1 illustrates the ANOVA of ADHD scores for 40 genes. Figure 1A-2 teaches TPH SNP A779C has a p values of 0.495. Figure 1A-3 teaches PNMT GNP G-148A has a p value of 0.129. Figure 1B-2 teaches ADORA2A C108T (Rsal) has a p-value of 0.229. Figure 1B-2 teaches NOS3 has a p value of 0.830. Finally, Figure 1B-3 teaches NAT1 T1088 have a p value of 0.329. It is noted that none of these p-values are significant at alpha= 0.05. Figure 2 appears to illustrate 22 genes when combined are associated with ADHD, however, it is unclear which 22 genes are involved in the analysis. Figure 3 appears to illustrate that each of TPH, PNMT, ADOA2A, NOS3 and

NAT1 have a p values <= 0.05 for ADHD. Thus, there is apparent confusion between Figure 3 and Figure 1. The specification teaches there were 326 unrelated, non-Hispanic Caucasians. 271 of the subjects have Tourette syndrome and 55 were controls (page 9, lines 20-25). The text of the specification teaches ADOA2A was significant at $p < 0.05$ (page 12, lines 15-18). Moreover, the specification teaches that "the only other new gene that produced a significant individual result was the NAT1 gene" (page 13, lines 10-11). With respect to NOS3, the specification teaches that NOS3 was significantly involved with all three traits" (page 15, lines 54-28).

The art teaches analysis of numerous genes in ADHD including ADOA2A, NAT1 and NOS3. Comings (Clin. Genet. Vol. 58, pages 31-40, July 2000) teaches each of these genes are not significantly associated with ADHD (Table 1). With respect to TPH, the art teaches there is a lack of association between the A218C polymorphism and ADHD in Chinese Han population. Tang (Am. J. of Med. Genetics, Vol. 105, pages 485-488, August 2001) teaches that the negative results of the study may be limited to the Chinese Han population or that the A218C polymorphism is not functionally significant and that some other variants are associated with ADHD (page 487, col 1-2).

The art also teaches that ADRA2A and ADRA2C genotypes are individually associated with ADHD (Comings et al. Clin. Genet. Vol. 55, pages 160-172, 1999, Table 2, page 165).

Comings et al. (AM. J. of Medical Genetics, Vol. 67, pages 264-288, 1996) teaches analyzing the additive effect of genes for ADHD. As seen in Figure 2, the listing of all possible combinations of the three markers is illustrated. The most densely

shaded area shows the part of the ADHD score that is diagnostic for ADHD. It is clear from figure 2 that each of the genes individually is not diagnostic of ADHD. It is only the combination of all three and the combinations of at least two. Therefore, the skilled artisan is clearly not enabled to detect ADHD using a single gene, as claimed by the instant claims.

Moreover, Blum (US Pat. 6,132,724, October 2000) teaches association of CHRNA4 gene with ADHD (Example 28, col. 306). Similarly, Blum teaches the additive effect of three adrenergic genes (ADRA2A, ADRA2C, DBH) on ADHD subjects (Example 27, col. 294).

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. Based upon the teachings in the specification, it is unclear how to interpret the data. For example, the figures appear to illustrate that the genes are both significant and not significant. Therefore, it is unclear what is being shown in the figures and whether the genes are significant alone, i.e. not in combination with other genes. Moreover, it is unclear whether each of the combinations of gene are significantly associated with ADHD, or whether only the combination of 22 genes is significantly associated with ADHD.

Additionally, the claims are drawn to detecting at least 2, 3, or 4 non-wild-type alleles in the recited genes. The claims have been amended to require particular mutations in four of the five recited genes. The claims do not require any particular non-wild type allele for NOS3. The specification has not described which non-wild-type alleles are associated with ADHD in NOS3 and which alleles are neutral polymorphism.

Numerous SNPs in the genome are known to be unassociated with diseases, especially with ADHD in particular. Therefore, the mere detection of a non-wild-type allele within NOS3 does provide indication that the subject is at an increased risk for ADHD. In order to practice the invention as broadly as claimed the skilled artisan would be required, unduly, to analyze NOS3 for alleles, determine whether they are wild-type or non-wild-type alleles and analyze the alleles for an association with ADHD. This trial and error experimentation is unpredictable. It is unpredictable whether the gene has alleles aside from the alleles studied in the instant application, whether these alleles are associated with ADHD, and whether the alleles confer an increased risk for ADHD or whether the alleles are protective and in fact are indicative of a decreased risk for ADHD. Moreover, the skilled artisan would be required to analyze numerous populations which are representative to determine whether the allele is associated with an increased risk over populations in general or whether the allele is associated within only certain populations. Moreover, the specification teaches that there are differences in associations between various ethnic or racial backgrounds (page 7). The specification has only sampled unrelated non-Hispanic Caucasians. The specification has not provided a broad based population study which would be representative of numerous populations.

Furthermore, with respect to the particular combination of genes, the specification fails to provide any evidence that this subsection of the 22 genes which were analyzed provides any association with ADHD. Detecting non-wild type allele

would not be necessarily indicative of ADHD, as all SNPs and alleles within genes are not all correlated with disease state.

Since the claims have been amended to now require two, three or four or more non-wild type alleles, evaluating the multiple regression data of the specification is essential. A review of multiple regression indicated the following information (Statistics, Richard Johnson, page 486-488, 1992). A response variable "y" may depend on multiple factors. When used alone, x fails to be a good predictor of y because of the effects of those other influencing variables. For example multiple linear regression would look at the yield of a crop which depends not only upon the amount of fertilizer but also on the rainfall and average temperature during growing season. Cool weather and no rain could completely cancel the choice of a correct fertilizer, for example. Thus, multiple regression refers to a model of relationship where the response depends on two or more predictor variables. If the response variable, for example ADHD, in an experiment is expected to be influenced by two input variables, for example non-wild type alleles of TPH and NOS3. This model suggests that aside form the random error, the response varies linearly with each of the independent variables when the others remain fixed. The instant specification does not provide any guidance as to whether particular combinations of non-wildtype alleles are associated with ADHD. It is unpredictable whether the particular combinations are associated with ADHD since the individual mutations in the genes are not significantly associated with ADHD. The teachings of the entire multiple regression does not appear to indicate that the particular combinations of 2, 3 or 4 genes are associated with ADHD. Specifically, the claims are

drawn to a method of detecting, for example a SNP at position 779 of TPH and NOS3. The instant specification teaches that The SNP at position 779 of TPH has a p-value of 0.495 and NOS3 has a p-value of 0.83. The instant specification fails to teach that the additive effect of these two non-wild type alleles are significant when in combination with each other such that they may be used to determine whether a subject is at risk for ADHD. Similarly, there is no teachings in the specification that any of the combinations of two, three or four alleles within the claim are associated with ADHD.

Without an indication that 2 or 3 or 4 or more of these five alleles provide significant association with ADHD, it is unpredictable that the skilled artisan could use these five alleles for detecting ADHD.

Therefore, based upon the analysis above, neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed.

Response to Arguments

The response traverses the rejection. The response asserts that the Examiner is not reading the data correctly despite the previous explanations (page 5 of response filed June 23, 2004). The response points out that the data in Figures 3 and 4 indicate particular recited polymorphisms are significant in their contribution to ADHD as determined by the disclosed methods. This argument has been reviewed but is not convincing because the brief description of the drawings for Figure 3 specifically states that the figure summarizes the results for individual genes that were included in the regression equation after all forty-two genes were entered as independent variables and the non-significant ones removed by backward elimination. An analysis of a

combination of 22 genes for ADHD would be expected to be more powerful than a single gene for detecting risk for ADHD. Figure 2, states that for ADHD, the p-value with 22 genes is highly significant. In the response filed December 23, 2002, page 6, the response states that Figure 1 is directed to individually selected and analyzed genes. The examiner relied upon such information that the genes were not individually associated with a risk for ADHD in the previous enablement rejection stating that it would be unpredictable how to detect risk based upon the genes individually since the specification specifically teaches no association exists. Further, Figure 3 is directed to a multivariate regression analysis by association of the candidate genes. This set of genes is analyzed with respect to the entire set.

While the specification appears to teach that a combination of 22 genes is positively associated with ADHD, there is no indication that non-wild type alleles from NOS3 and TPH, for example, would enable the skilled artisan to detect an individuals risk for ADHD for the reasons already of record and those discussed above.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

7. No claims allowable.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
August 17, 2004